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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/618,178	07/18/2000	Stephen E. Lincoln	13020-10	9015

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EXAMINER
FREDMAN, JEFFREY NORMAN

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 04/28/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/618,178	LINCOLN ET AL.	
	Examiner	Art Unit	
	Jeffrey Fredman	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 February 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *51-54 and 56-95* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *51-54 and 56-95* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *14* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status

Claims 51-54 and 56-95 are pending.

Claims 51-54 and 56-95 are rejected.

Any rejection which is not reiterated in this action is hereby withdrawn as no longer applicable.

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on February 28, 2003 has been entered.

Priority

1. Applicant's claim of priority back to application 08/173,173, 07/775,786 and 07/664,837 is noted. The examiner was unable to determine whether these applications provide support for the entirety of the current claims and therefore the claims are given the effective date of the immediate parent 09/088,820, which provides express support (except for claim 50, as detailed below).

Claim Rejections - 35 USC § 102

2. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

3. Claims 51-54 and 69-74 are rejected under 35 U.S.C. 102(b) as being anticipated by Kimpton et al (PCR Meth. Appl. (August 1993) 3:13-22).

Kimpton teaches a method of determining the genotype at a locus within genetic material obtained by PCR amplification (page 14) comprising:

a) assembling reaction value data points for the samples, each reaction-value data point corresponding to a respective one of the samples and including at least one reaction value (here the data points represented by each of the separate peaks in figure 1 represents a different sample and are assembled in figure 2) (see pages 14-16),

b) determining an initial conditional probability for each reaction value data point for each genotype (here, the data was initially analyzed by analyzing the bands, to establish a conditional probability for reaction value (see page 15, subheading "statistical calculations and figure 1),

c) computing a conditional probability of each genotype for each reaction value data point (here, the calculation of band sizing determined the allele to which the sample belonged, thereby determining a genotype, since a genotype is composed of particular alleles at particular positions, see page 16, columns 2 and 3 and page 17, table 2)

d) determining the genotype and confidence score for each reaction value data point, thus determining the genotype and confidence score at the genetic locus for each

sample (here, table 2 on page 17 provides for each reaction point the genotype and a standard deviation based on the data obtained from step d) (page 16 and page 17).

Kimpton expressly teaches reacting the material at multiple loci (page 14, table 1). On page 17, Kimpton expressly considers multiple alleles in the probability distributions, particularly in table 2 which expressly notes that the method is applicable to any number of alleles. Kimpton expressly teaches the use of multiple data points derived from multiple runs of the automated apparatus including multiple data sets in the exemplified method and apparatus (page 16, especially figure 2). Kimpton expressly teaches that the locus may be dinucleotide or tetranucleotide repeats (page 13). Kimpton expressly selected the loci for their discrimination ability and teaches that several different loci may be analyzed (page 16, column 1).

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

6. Claims 51-54 and 60-74 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kimpton in view of Clark et al (Mol. Biol. Evol. (March 1990) 7(2):111-122).

Kimpton teaches the methods of claims 51-54 and 69-74 as discussed above. Kimpton does not teach modification of the data to iteratively improve the assay.

Clark teaches a method of resolving ambiguities by performing an iterative cascade of improvements on the data points (abstract and pages 111-113). Clark also applies the method to restriction site polymorphisms.

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine the iterative screening and improvement methods of Clark with the probability method of Kimpton since Clark states "Details of the algorithm for extracting allellic sequences are presented here, along with some population genetic considerations that influence the likelihood of success of the method. The algorithm also applies to the problem of inferring haplotype frequencies of closely linked restriction site polymorphisms (abstract)". An ordinary practitioner would have been motivated to apply the conceptual idea of iterative data processing of Clark in the genotyping method of Kimpton in order to extract the as close to the entirety of the allelic sequences as possible. Further, an ordinary practitioner would have recognized that the method could be performed using any length marker, including single nucleotide polymorphisms such as the restriction site polymorphisms expressly discussed and motivated by Clark.

7. Claims 51-54 and 56-74 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kimpton in view of Clark et al (Mol. Biol. Evol. (March 1990) 7(2):111-122) and further in view of Goelet et al (WO 92/15712).

Kimpton in view of Clark teaches the methods of claims 51-54 and 60-74 as discussed above. Kimpton in view of Clark does not teach genetic bit analysis, which includes allele specific amplification.

Goelet teaches genetic bit analysis methods, including allele specific amplification methods (see entire document, expecially pages 10-13).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine the method of Kimpton in view of Clark with the use of genetic bit analysis or allele specific amplification to develop the data since Goelet states "The current invention provides a method that can be used to diagnose or characterize nucleic acids in biological samples without recourse to gel electrophoretic size separation of the nucleic acid species. This feature renders this process easily adaptable to automation and thus will permit the analysis of large numbers of samples at relatively low cost (page 8, lines 27-33)". An ordinary practitioner would have been motivated to substitute the equivalent genetic bit analysis method for PCR in order to minimize the need for gel electrophoresis and enhance the automatability of the process as expressly motivated by Goulet in order to speed analysis and minimize costs.

8. Claims 51-54, 56, 58 and 60-74 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kimpton in view of Clark et al (Mol. Biol. Evol. (March 1990) 7(2):111-122) and further in view of Backman et al (U.S. Patent 5,516,663).

Kimpton in view of Clark teaches the methods of claims 51-54 and 60-74 as discussed above. Kimpton in view of Clark does not the use of ligation chain reaction.

Backman teaches a method of LCR (abstract).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine the method of Kimpton in view of Clark with the use of LCR as taught by Backman since Backman states "One of the great strengths of amplification reactions is their ability to detect exceedingly small numbers of target molecules (column 2, lines 8-10)". An ordinary practitioner would have been motivated to substitute LCR for the equivalent amplification method of PCR for the express motivation that LCR can detect small numbers of target molecules and because LCR is a known equivalent amplification assay to the PCR used by Kimpton.

New Grounds of Rejection based on New claims

9. Claims 75-83, 85, 86, 88, 89, 91-93 and 95 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kimpton et al (PCR Meth. Appl. (August 1993) 3:13-22) in view of Ledwina et al (Biometrics (1980) 36:161-165) and further as motivated in view of JeanPierre (Ann. Hum. Genet. (1992) 56:325-330).

Kimpton teaches a method of determining the genotype at a locus within genetic material obtained by PCR amplification (page 14) comprising:

a) Reacting the material at the locus to produce a first reaction value (see page 14, columns 1-3, subheading "Locus specific amplification conditions"),

b) forming a data set including the first reaction value by assembling reaction value data points for the samples, each reaction-value data point corresponding to a respective one of the samples and including at least one reaction value (here the data

points represented by each of the separate peaks in figure 1 represents a different sample and are assembled in figure 2) (see pages 14-16),

e) determining the genotype and confidence score for each reaction value data point, thus determining the genotype and confidence score at the genetic locus for each sample (here, table 2 on page 17 provides for each reaction point the genotype and a standard deviation based on the data obtained from step d) (page 16 and page 17).

With regard to claim 77 and 78, Kimpton expressly teaches reacting the material at multiple loci (page 14, table 1). With regard to claims 80-82, on page 17, Kimpton expressly considers multiple alleles in the probability distributions, particularly in table 2 which expressly notes that the method is applicable to any number of alleles. Kimpton expressly teaches the use of multiple data points derived from multiple runs of the automated apparatus including multiple data sets in the exemplified method and apparatus (page 16, especially figure 2). Kimpton expressly teaches that the locus may be dinucleotide or tetranucleotide repeats (page 13). Kimpton expressly selected the loci for their discrimination ability and teaches that several different loci may be analyzed (page 16, column 1).

While Kimpton uses the Hardy-Weinberg test, Kimpton does not establish a distribution set of probability distributions and Kimpton does not then apply the reaction value of the distributions to detemine a measure of a conditional probability of each genotype of interest at the locus.

Ledwina teaches a method in which genotypes can be determined in which the Hardy Weinberg test is modified such that the steps of:

c) establishing a distribution set of probability distributions and associating hypothetical values with corresponding probabilities for each genotype of interest (see page 162 and page 163),

d) applying the first value to each pertinent probability distribution to determine a measure of conditional probability of each genotype of interest (see page 162 and page 163, especially "conditional distribution of T given Z=z" equation on page 163).

With regard to claim 76 and 79, Ledwina teaches a plurality of distributions which are hypothetical (see page 162, "common probability distribution of (T,Z) is multinomial with 1/2m(m+1) cells and with the vector of cell probabilities g=(g...).".

Further, JeanPierre motivates the use of computation of unknown genotypes to analyze the conditional probabilities relative to a distribution of hypothetical reaction values (see page 330).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Kimpton to use the conditional probability distribution method of Ledwina since Kimpton notes that the anlaysis uses the Hardy-Weinberg equilibria (see abstract) and since Ledwina states "The class of admissible tests for Hardy-Weinberg equilibrium in a multi allelic system is charactgerized. The standard goodness of fit chi square test is shown to be admissible for systems of two or more alleles. The conditional probability distribution required to determine the exact significance level of this test is presented (see abstract)". An ordinary practitioner would have been motivated to apply this hypothetical distribution analysis to genotyping since Jeanpierre notes the gains from creating such a

distribution include avoiding hazards such as incorrectly using the simple average of the conditional probabilities instead of the harmonic mean, to more accurately determine the genotype (see page 330).

10. Claims 75-86, 88, 89, 91-93 and 95 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kimpton et al (PCR Meth. Appl. (August 1993) 3:13-22) in view of Ledwina et al (Biometrics (1980) 36:161-165) and further as motivated in view of JeanPierre (Ann. Hum. Genet. (1992) 56:325-330).

Kimpton in view of Ledwina as motivated by JeanPierre teach the limitations of claims 75-83, 85, 86, 88, 89, 91-93 and 95 as discussed above. Kimpton in view of Ledwina as motivated by JeanPierre do not teach interation of the method.

Clark teaches a method of resolving ambiguities by performing an iterative cascade of improvements on the data points (abstract and pages 111-113). Clark also applies the method to restriction site polymorphisms.

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine the iterative screening and improvement methods of Clark with the probability method of Kimpton in view of Ledwina as motivated by JeanPierre since Clark states "Details of the algorithm for extracting allellic sequences are presented here, along with some population genetic considerations that influence the likelihood of success of the method. The algorithm also applies to the problem of inferring haplotype frequencies of closely linked restriction site polymorphisms (abstract)". An ordinary practitioner would have been motivated to apply the conceptual idea of iterative data processing of Clark in the genotyping method of Kimpton in view of Ledwina as motivated by JeanPierre in order to extract the as close to the entirety of the allelic sequences as possible. Further, an ordinary practitioner

would have recognized that the method could be performed using any length marker, including single nucleotide polymorphisms such as the restriction site polymorphisms expressly discussed and motivated by Clark.

11. Claims 75-83 and 85-95 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kimpton et al (PCR Meth. Appl. (August 1993) 3:13-22) in view of Ledwina et al (Biometrics (1980) 36:161-165) and further as motivated in view of JeanPierre (Ann. Hum. Genet. (1992) 56:325-330).

Kimpton in view of Ledwina as motivated by JeanPierre teach the limitations of claims 75-83, 85, 86, 91-93 and 95 as discussed above. Kimpton in view of Ledwina as motivated by JeanPierre does not teach genetic bit analysis, which includes allele specific amplification, nor the particular alleles listed.

Goelet teaches genetic bit analysis methods, including allele specific amplification methods (see entire document, expecially pages 10-13). Goulet teaches single specific nucleotide alleles (see page 40, example 3). Goulet also shows a mutation which is associated, at least indirectly, with a restriction site (see figure 2).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine the method of Kimpton in view of Clark with the use of genetic bit analysis or allele specific amplification to develop the data since Goelet states "The current invention provides a method that can be used to diagnose or characterize nucleic acids in biological samples without recourse to gel electrophoretic size separation of the nucleic acid species. This feature renders this process easily adaptable to automation and thus will permit the analysis of large numbers of samples at relatively low cost (page 8, lines 27-33)". An ordinary practitioner would have been motivated to substitute the equivalent genetic bit analysis method for PCR in order to

minimize the need for gel electrophoresis and enhance the automatability of the process as expressly motivated by Goulet in order to speed analysis and minimize costs.

Response to Arguments

12. Applicant's arguments filed February 28, 2003 have been fully considered but they are not persuasive.

Applicant argues that the 102 rejection of claims 51-54 and 69-74 which relies upon the Kimpton reference has been overcome by amendment. No amendment to claim 72 was found in the application. Applicant restates the steps of claims 72 and then concludes that the method is not disclosed by Kimpton. No particular reasons are given why claim 72 has overcome the Kimpton reference. A review of the rejection finds that all of the limitations of the claims rejected are met by Kimpton, so this rejection is maintained.

Applicant then argues the 103 rejections. With regard to the 103 rejection of Kimpton in view of Clark, Applicant simply argues that Kimpton is insufficient. However, as already noted, Kimpton properly meets the limitations of the claims. Applicant has presented essentially no actual argument, as opposed to simple conclusory statements, as to why Kimpton is not a proper rejection. Therefore, the 103 rejection in view of Clark will be maintained.

13. In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the

references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, specific motivation is cited in the rejection itself. Further, the argument that Kimpton was satisfactory for it's purpose is not an argument that addresses the motivation. Every reference states that it achieves the goals set out. If this argument was found persuasive, it would subvert the congressional intent in enacting section 103 of title 35, since every reference is complete in itself and no obviousness rejections would ever be made.

With regard to the final 103 over Backman, Applicant again argues that Kimpton is insufficient. As this argument is not persuasive, the 103 rejection is maintained.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey Fredman whose telephone number is 703-308-6568. The examiner can normally be reached on 6:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 703-308-1119. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Jeffrey Fredman
Primary Examiner
Art Unit 1634

April 27, 2003